**RNA Toxicity hypotheses in Trinucleotide Repeat expansion disorders and FXTAS**

1. Mechanism of the effects of RNA in nucleotide expansion in 4 hypotheses:
   1. **Sequestration model**
      1. This hypothesis suggests that the secondary structures formed by the repeat expanded transcript binds RNA binding proteins essential for other functions such as splicing, transport, and processing
         1. Causes the RNA binding proteins to not interact with other RNA molecules within the cells
   2. **Abnormal activation of signaling model**
      1. It is thought that these repeat sequences form hairpin loops
         1. These hairpins activate dsRNA dependent kinases
            1. The dsRNA dependent kinases activate protein kinases
   3. **Aberrant RNA splicing model**
      1. These nucleotide repeats in the RNA from transcription can lead to the disruption or change of mRNA splicing
         1. This may cause a shortened protein, a larger protein, a smaller protein, or no protein at all
   4. **Antisense transcription model**
      1. Antisense transcripts are very common in the genome
      2. May have roles in RNA stability and transcriptional regulation
      3. Antisense transcripts that include the expansion may result in a translated protein with a polygultamine expansion that will aggregate
      4. Antisense transcripts may also modify RNA stability of the mRNA that results in the toxic product
2. Clinical Manifestations of Fragile-X associated Tremor/Ataxia Syndrome (FXTAS):
   1. Is late onset
   2. Usually affects older adult carriers for the pre-mutation
   3. One of the most common single gene late onset disorders
   4. This is displayed as neurodegeneration throughout the cortex and cerebellum
      1. Inclusions accumulate in neuronal and glial nuclei
         1. Inclusions contain FMR1 mRNA and a number of proteins
            1. These proteins are involved in other RNA processing modalities such as splicing
   5. Progressive intention tremor
   6. Gait ataxia
   7. May look like Parkinson’s in some aspects
   8. May have cognitive delay which progresses to dementia
   9. Peripheral neuropathy
   10. Dysautonomia
   11. Some evidence of autoimmune dysfunction in women
   12. Protein-RNA inclusion in the nucleus is evident upon staining
3. Differences between FXTAS and Fragile-X Syndrome:
   1. Fragile X-syndrome results in the expansion of the CGG repeat to >200 repeats
      1. This causes silencing of transcription by methylation at CpG islands
         1. Means no function FMR Protein
   2. FXTAS
      1. This is cause by an expansion of the same region in FMR1 gene that causes Fragile-X syndrome
      2. This repeat is between 50 and 200 hundred which is indicative of the pre-mutation
         1. This results in active transcription of the gene
         2. Thought that the RNA transcript forms secondary structures which reduces translational efficiency
4. Role of RNA in FXTAS (Also see Abnormal activation of signaling model):
   1. Shows elevated FMR1 mRNA
   2. The mRNA that is transcribed from the pre-mutation FMR1 gene causes the sequestering of other proteins (Pur alpha and hnRNPA2/B1)
      1. These proteins are involved in other cellular processes that process RNA
         1. hnRNPA2/B1 = RNA splicing
         2. Pur alpha = RNA and DNA binding protein that binds to rCGG repeats
   3. Transcribed anti-sense RNA in a greater proportion than the sense transcript may result in toxic events